Peroxovanadium-mediated protection against murine leishmaniasis: role of the modulation of nitric oxide.

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The phosphotyrosine phosphatase inhibitor bpV(phen) has the ability to markedly decrease the progression of leishmaniasis in vivo. Here, we have identified the mechanisms that are responsible for this protective effect. We report that two potei peroxovanadium (pV) compounds, bpV(phen) and bpV(pic), control progression o leishmaniasis in a similar manner by modulating NO-dependent microbicidal action. We observed that their injection can rapidly and transiently induce the expression of inducible NO synthase (iNOS) in livers of mice and enhance circulating nitrate levels. Treatment of mice with bpV(phen) or bpV(pic) complete controlled progression of leishmaniasis in an NO-dependent manner, since inhibition of iNOS with aminoguanidine completely reversed this pV-mediated protection. This NO-dependent pV-mediated protection was further demonstrated by the incapacity of bpV(phen)-treated Nramp-/-, iNOS-/- mutant mice to control Leishmania major infection. Using an air pouch model, we showed that bpV(phen) can strongly modulate secretion of L. major-induced pro-inflammatory molecules and neutrophil recruitment. In addition, we observed that bpV(phen) per se can strongly induce the expression of Th1 type cytokines over Th2 in spleens of animals. Overall, this study has allowed us to establish the in vivo functional and immunological events involved in pV-mediated protective mechanism against leishmaniasis and that NO plays a pivotal role in this process.

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